REMARKS

Claim 1 has been amended

(1) to clarify that the construct can be used to deliver an immunogen either directly (the construct comprises the actual immunogen) or indirectly (the construct comprises an expressible nucleic acid which encodes an immunogen; the cells of the recipient express the nucleic acid and thereby produce the immunogen in situ, with basis at P16, L23 to P17, L9);

(2) to require at least one cationic sterol (basis at P28, L23 "cationic ISCOM" and P39, L19 "DC-cholesterol; note also that only a cationic or anionic species can engage in electrostatic interaction as contemplated by P29, L14);

(3) to refer to a "nucleic acid" rather than a "genetic determinant" with basis at P16, L23-31 and P17, L1-19;

(4) to delete "contacting groups" which in turn rendered superfluous the first/second distinction.

Basis for the new claims is as follows:

38: "such as" clause in original claim 13.

39: P12, L26-27.

40: P20, L8-21, L19; P21, L22-26; P21, L29-30.

41: P19, L20-P20, L2

42: "Preferably" clause in original claim 20.

43: since claim 1 can comprise "immunogen" or "nucleic acid".

44: original claim 26(i) and (ii).

45: original claim 26(ii).

46-47: original claim 26(iii); P16, L23-P17, L12

48: P39, L19

49: See PCT/DK02/00229, incorporated by reference at P28, L25-27, and "cholesterol" at P39, L11; cp. P30, L10-14.

50-51: P39, L11.

52: P39, L12.
53: P39, L15.
54: P39, L20.
55: P39, L13-14 and 19.
56-57: P14, L14; cp. P40, L21-23.
58-59: P29, L28-P30, L3.
60: original claim 26(iv).
61: P12, L27-30.

1. Definiteness Issues (OA pp. 3-4)

The examiner has made several rejections, criticizing terms of claims 1, 17, 18 and 24 as "vague and indefinite". The examiner doesn't explain precisely what it is objectionable about these terms. To say that "it is impossible to determine the metes and bounds of the claimed invention" is merely to restate the conclusion that the term is "indefinite".

Several of the questioned terms are defined in the present specification, or in the specification of WO 020981 (US patent application No. 10/114.957). WO 020981 is the PCT publication of PCT/DK02/00229, first cited in the present specification at page 4, line 5, and formally incorporated by reference at page 28, lines 25-27. Consideration should also be given to definitions appearing in common text books or on the internet.

1.1. Claim 1 (Genetic determinant)

A genetic determinant is a nucleic acid (DNA or RNA) which acts as or codes for an immunogenic determinant. Claim 1 has been amended to recite delivery of an immunogen or an expressible nucleic acid which encodes the immunogen, and the term "genetic determinant" has been excised.

The term "genetic determinant" is formally defined in WO 020981, page 21, as follows:

"Genetic determinant: Genetic determinant refers to nucleotides and polynucleotides, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The genetic determinant may be made by synthetic chemical methodology known to one of ordinary skill in the art, or by the use of recombinant technology, or by a combination thereof. The DNA and RNA may optionally comprise unnatural nucleotides or nucleotide derivatives including LNA (locked nucleic acids) and PNA (peptide nucleic acids), and it may be single or double stranded. "Genetic determinant" also refers to sense and anti-sense DNA and RNA, which are nucleotide sequences which are complementary to specific sequences of nucleotides in DNA and/or RNA."

Immunogenic determinants, in turn, are defined by the present application at Page 25, line 5: "Immunogenic determinants denote any substance capable of raising an immune response, including a specific antibody response." This definition is supported by external literature, e.g.,

1. Antigenic determinant: the part of an antigen molecule that binds to the antigen-binding region of an antibody; also called epitope (*Glossary, Molecular biology, Lodish, 3rd Ed*).
2. Antigenic determinant: epitope (*http://www.merriam-webster.com/dictionary/antigenic*).

Page 16, lines 23-31 of the present application teaches that the immunogen or antigen may comprise "a nucleic acid sequence". However, it is not intended that the nucleic acid sequence is necessarily the actual immunogen. Rather, as taught by page 17, lines 1-12:

> Preferably, the nucleic acid sequences may encode a polypeptide and/or peptide. When the nucleic acid sequence encodes a polypeptide and/or a peptide, preferably, the polypeptide and/or peptide and/or fragments thereof constitute the compound,

> which is recognised by the immune response.
>
> Accordingly, the following scenario may take place:
>
> i) Nucleic acid sequences are targeted to the target cell
>
> ii) Nucleic acid sequences are internalised into the target cell
>
> iii) Polypeptides and/or peptides are produced within the target cell
>
> iv) Polypeptides and/or peptides and/or fragments thereof are displayed at the cell surface.

The displayed polypeptides comprise foreign epitopes, see page 17, lines 14-16, and therefore elicit an immune response.

1.2. Claim 1 (Electrostatic interaction)

The term is generally known and understood in the art. The term "electrostatic interaction" is defined by WO 020981, page 20:

> Electrostatic interaction: Any interaction occurring between charged components, molecules or ions, due to attractive forces when components of opposite electric charge are attracted to each other. Examples include, but are not limited to: ionic interactions, covalent interactions, interactions between a ion and a dipole (ion and polar molecule), interaction between two dipoles (partial charges of polar molecules), hydrogen bonds, i. e. hydrogen bonded to e. g. i) a nitrogen atom, an oxygen atom, or a fluor atom in one molecule, while at the same time being bonded to ii) a nitrogen atom, an oxygen atom, or a fluor atom in another molecule or the same molecule, interchelating interactions, and London dispersion bonds (induced dipoles of polarizable molecules). Thus, for example, "ionic interaction "or" electrostatic interaction" refers to the attraction between a first, positively charged molecule and a second, negatively charged molecule. Ionic or electrostatic interactions include, for example, the attraction between a negatively charged bioactive agent, for example, a genetic determinant, and one or more of i) a

> positively charged lipid, for example, a cationic lipid, ii) a positively charged saponin, for example a cationic saponin, and iii) a positively charged sterol, for example a cationic sterol.

The glossary for *Nature Reviews: Microbiology*, defines "Electrostatic interactions" as being "between charged molecules or atoms", see http://www.nature.com/nrmicro/journal/v3/n11/glossary/nrmicro1265_glossary.html.

See David S. Goodsell, Bionanotechnology: Lessons from Nature p. 87 (2004).

1.3. Claim 1 (Hydrophobic interaction)

The term is generally known and understood in the art. A "hydrophobic interaction" is defined by WO/ 020981, page 21, as follows:

> Hydrophobic interaction: Any interaction occurring between essentially non-polar (hydrophobic) components located within attraction range of one another in a polar environment (e. g. water). As used herein, attraction range is on the scale of about 100 nm. A particular type of hydrophobic interaction is exerted by "Van der Waal's forces", i. e. the attractive forces between non-polar molecules that are accounted for by quantum mechanics. Van der Waal's forces are generally associated with momentary dipole moments which are induced by neighboring molecules and which involve changes in electron distribution.

The Free Dictionary by Farlex, (http://medical-dictionary.thefreedictionary.com/Hydrophobic+interaction) cites definitions from various established dictionary sources.

Thus, it notes that

1) Saunders Comprehensive Veterinary Dictionary, 3 ed. 2007

defines "hydrophobic interaction" as "interaction of nonpolar (un-ionizable) hydrocarbon molecules forced together because of stronger water-water interaction."

2) Mosby's Medical Dictionary, 8th ed. 2009 defines "hydrophobic" as "pertaining to the property of repelling or preferentially excluding water molecules, a quality possessed by nonpolar radicals or molecules that are more soluble in organic solvents than in water".

3) Mosby's Dental Dictionary, 2d ed., 2008, defines "hydrophobic" as "the resistance of a substance to combine with water. Hydrophobic substances, such as oil, are composed of nonpolar molecules, which tend to clump together and repel water."

A similar definition of "hydrophobic interaction" appears in Janeway and Travers , Immunobiology- the immune system in health and disease, page 3:10 (3rd ed, **[need year]**).

ChemiCool, "Definition of hydrophobic interaction," http://www.chemicool.com/definition/hydrophobic_interaction.html defines it as "The tendency of hydrocarbons (or of lipophilic hydrocarbon-like groups in solutes) to form intermolecular aggregates in an aqueous medium, and analogous intramolecular interactions. The name arises from the attribution of the phenomenon to the apparent repulsion between water and hydrocarbons. However, the phenomenon ought to be attributed to the effect of the hydrocarbon-like groups on the water-water interaction."

The glossary for *Nature Reviews: Microbiology*, defines "hydrophobic interactions" as being "Interactions that rely on the tendency of non-polar groups to aggregate to avoid contact with a polar solvent."

1.4. Claim 1 (Contacting Group)

While we do not agree with the examiner that "contacting group" is indefinite, the issue is moot as this term has been removed from the claims.

1.5. Claim 17: Immunogen and/or immunogen delivery system is separated from each other"

The term "immunogen" is of course well understood in the art, and immunogens are further discussed at pp. 13-14. The "immunogen delivery system" is the "PosIntro or ISCOM", see page 4, lines 27-30, and is taught to comprise "at least one saponin and at least one sterol", see page 5, lines 10-11. Both the immunogen and the immunogen delivery system are associated with an "occlusion vehicle", see above.

The specification first describes an embodiment in which the "immunogen and the immunogen delivery system are distributed in the occlusion vehicle and this distribution is preferably homogeneously", see page 11, lines 4-7 and figure 1.

Second, it describes an embodiment in which "the immunogen and the immunogen delivery system" are "distributed on the surface of the occlusion vehicle", see page 11, lines 9-10.

Third, there is an embodiment in which the immunogen and the immuongen delivery system are "embedded in a non-adherent vehicle" which is "activated just before use", see page 11, lines 24-28.

Finally, there is the embodiment of claim 17, in which "The immunogen and the immunogen delivery system are ... separated from each other." See page 13, line 4-5. Any embodiment were the immunogen and the immunogen delivery system is separated, regardless how, is claimed.

1.6. Claim 18: Enhancer

According to the specification, Page 12, lines 17-19: "Enhancers in the context of penetration through skin and mucosa are a group of compounds that facilitates the transport of drugs or vaccines over skin or mucous membranes". The meaning of the term can also be inferred from the listing of typical enhancers which appears at page 12, lines 26-30. Thus, the specification defines the word "enhancer".

1.7. Claim 24 ("Construct according to claim 19, wherein the at least one immunogen is selected in such a way that the induced immunological response may act upon subsequent exposure of the individual to said pathogenic microorganism.")

Claim 24 has been cancelled.

2. Prior Art Issues

2.1. Anticipation (OA sec. 4)

Claims 1, 2, 4, 5, 9, 10, 13, and 16-27 stand rejected as anticipated by Foldvari (WO 99/11247)(D2 in the international search report).

The examiner asserts that Foldvari's composition comprises an immunogen, an occlusion vehicle, and an immunogen delivery system comprising both a sterol and a saponin. With regard to the delivery system, the examiner states that Foldvari discloses "lipid vesicles" (citing page 14, lines 13-15) and states that "in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols and saponin (see page 8, lines 17-19 and 21; page 12, line 6)."

Immunogen Delivery System

We agree that Foldvari, page 8, lines 21-22 makes reference to

"glycolipids, ceramides and **sterols**, such as cholesterol....", and that Foldvari, in discussing "adjuvant activators" at page 12, lines 5-7, makes reference "to **saponin**, lysocethin, retinal, **Quil A** and pluronic polymer formulations...." (Quil A itself is a mixture of neutral saponins.)

However, claim 1 now requires that the construct comprise a **cationic** sterol. Foldvari does not disclose or suggest cationic sterols.

Also, according to D2, page 10, line 16, the size of the residues is 0.1 to 100 μm[1]. They are thus, at a minimum 100 nm. Hence, they are distinguished by new claim 56, which sets an upper limit of 50 nm.

The lipid vesicle in Foldvari is as indicated in the claims a suspension having a central core compartment containing an oil-in-water emulsion, and entrapped in the biphasic lipid vesicles, an immunogen. The lipid vesicles are illustrated in figure 1 and described in details on page 6 of D2 (lines 1-20). As appears, the entrapment of the immunogen is based on physico-chemical conditions within the vesicles, and the hydrophilic characteristics of the immunogen decide the place of entrapment.

Claim 58 requires that the complexes be in the form of microparticles with a rigid structure, and claim 59 that the structure be cage-like. This rigid structure is formed due to self-organizing inherent properties of the saponin component.

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[1] Line 17 says that 0.5-25 um is preferred. However, at page 15, lines 1-4, we have: "Typically, the pores of the membrane have a diameter slightly larger than the diameter of the lipid vesicles. In preferred embodiments, the membrane has pores in the size of 0.1-500 um, more preferably between 0.1-200 um." And at page 16, L8, "Biphasic lipid vesicles of about 0.5-10 um were obtained."

The lipid vesicle in D2 does not necessarily comprise saponins; D2 merely teaches that an adjuvant, which may be a saponin, may be incorporated into the vesicle, and thus implies that the versicle is formed without the saponin's assistance. Hence, the PosIntro complexes are structurally not related to lipid vesicles.

Immunogens

We do not dispute that Foldvari discloses immunogens, including nucleic acids. However, Foldvari does not specifically disclose nucleic acids which are chosen because they encode an immunogenic protein, as opposed to because of their immunogenicity qua nucleic acids, see new claims 46 and 47.

Occlusion Vehicle

The term "occlusion vehicle" as defined at applicants' page 4, lines 13-24 refers to a covering of skin or mucosal surface which limits water vapor transmission to the degree disclosed therein. There is no reference to vapor or gas transmission, or occlusion thereof, anywhere in the Foldvari disclosure. Water is mentioned only in the context of "oil-in-water emulsion" or the contents of the water phase of that emulsion.

The examiner states that Foldvari's "backing layer serves as a protective, impermeable covering to prevent loss of contents". It is true that Foldvari teaches "a reservoir 42 defined by an impermeable backing layer 44 and a membrane 46." However, it appears that what Foldvari means by "impermeable" is liquid impermeable, because the "reservoir contents" are liquid. (The emulsion is described as "a milky solution having the consistency of water".) The backing layer complements the membrane, which permits "diffusion of the reservoir contents" yet "functions to prevent bulk flow of the reservoir contents from the device". (emphasis added)

Hence, Foldvari does not clearly disclose an occlusion (limited water vapor permeability) vehicle as required by claim 1.

2.2. Obviousness (OA pp. 7-16)

Claims 1, 2, 4-6, 9, 10, 13, 16-27, and 32-34 stand rejected as obvious over Foldvari in view of British Pharmacopoiea. Claims 1, 2, 4, 5, 7-9, 10, 13, 16-27 and 32-34 stand rejected as obvious over Foldvari and Lee. Foldvari has already been discussed. British Pharmacopoiea is cited merely for hydrocolloid dressings. Lee is cited merely to show use of hydrogens as drug carriers.

2.2.1. As previously explained, the prior art does not suggest use of a cationic sterol, as now required by claim 1.

2.2.2. Vis-a-vis claims 55-58, the Posintro complex of 5 to 50 nm is much smaller than the lipid vesicles of Foldvari (being typically between 0.1 and 100 μm), but it is still - surprisingly - able to complex with proteins of rather large size, as also explained in the description, page 4, lines 8-20. Furthermore, the Posintro is a chemical complex without a central compartment, and the delivery effect on the immunogen is not related to any oil-in-water emulsion.

The adjuvant effect of the Posintro in based on the fact that it can form a complex in nano size with the immunogen/protein, which can permeate the skin and reach the target cells, in spite of the size of the complex. This is in itself surprising.

In contrast to this, there is no indication in Foldvari that the lipid vesicles can permeate the skin or cell membrane, and this is also very unlikely considered the size of the vesicles. In fact it is stated on page 11, lines 11-20, that a

permeation enhancer to enhance the penetration of the entrapped antigen may be included in the vesicles. But even if the lipid vesicles may be used for transport of an immunogen/protein by permeation of the skin, the present invention provides an alternative solution.

Hence, the claims are not obvious over the cited art.

2.2.3. Claims 1, 2, 4-6, 9, 10, 13, 16-27, 32-34 stand rejected as obvious over Foldvari (WO99/11247) and British Pharmacopoeia 1993 (Surgical Materials, 1996; 1943-4).

The examiner concedes that Foldvari et al. "do not specifically disclose the use of a hydrocolloid adhesive or that one of the two compartments comprises a lyophilized pad comprising the immunogen and the other compartment comprises water or other appropriate solvent/diluent." (OA p. 11).

British Pharmacopoeia is cited as disclosing "wound dressings and medicated bandages, which include a semipermeable hydrocolloid dressing (see page 1943)." However, it fails to remedy the deficiencies of Foldvari as discussed in the context of anticipation.

2.2.4. Claims 1, 2, 4, 5, 7-9, 10, 13, 16-27, and 32-34 stand rejected as obvious over Foldvari and Lee (2001).

The examiner concedes that Foldvari et al. "do not specifically disclose the use of a hydrocolloid adhesive, cross-linked or otherwise, nor do they disclose that one of the two compartments comprises a lyophilized pad comprising the immunogen and the other compartment comprises water or other appropriate solvent/diluent." (OA p. 15).

Lee is said to "disclose that hydrogels have been widely used

as a drug carrier (see page 10; section 3.5)". However, it fails to remedy the deficiencies of Foldvari as discussed in the context of anticipation.

3. Election/Restriction

Since the amended claims are allowable, dependent process claims should now be rejoined in accordance with MPEP 821.04.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\u-z\Zacc\Kirkby3\kirkby3.pto amendment.wpd